SCIENCE AND REGULATION

Filling gaps in science exposes gaps in chemical regulation

Examination of U.S. and EU regulatory systems raises more questions than answers

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The regulation of chemicals should protect public health and the environment from undue risk of harm, should promote the development and use of safer alternatives to more hazardous chemicals, and should provide the public with sufficient information to understand how well chemical risks are being managed. How well are these goals being achieved? The regulatory system in the United States has been derided as dysfunctional (*1*), even with major amendments enacted in 2016 (*2*) that some supposed would bring the U.S. program closer to the European Union's REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation. To build on the literature that documents the shortcomings of chemical regulation (*1*, *2*), we take as a convenient example the compounds described in new research by Washington *et al.* on page 1103 (*3*). Washington *et al.* report the unexpected presence in environmental samples of chloroperfluoropolyether carboxylate compounds (ClPFPECAs), apparently used as a substitute for other perfluoroalkyl substances (PFASs) that had raised environmental concerns (*3*). Attempting to trace these compounds through the regulatory regime raises more questions than answers, revealing the structural limits of existing regulation. These limits apply not only to this particular case but to myriad chemicals. How much confidence do regulatory systems give the public that substitute chemicals are safer than the substances they replace? Not nearly as much as one would like.

BIRTH OF A NEW CHEMICAL

The compounds found by Washington *et al.* apparently were first reported in the literature as part of the search for "environmentally friendly" replacements for chlorofluorocarbons and hydrofluorocarbons (*4*). They appear to have found a use, however, in the manufacture of fluorinated polymers with nonstick properties for use, for example, in cookware (*5*, *6*). As such, they helped answer an urgent desire to eliminate the use and release of perfluorooctanoic acid (PFOA) and its precursors and homologs (*3*), which had been widely dispersed in the environment as a result of the production of other substances with similar properties [see supplementary materials (SM)]. Amid growing evidence that PFOA and similar compounds were highly persistent, bioaccumulative, and potentially toxic, as well as a spate of private lawsuits and increasing state and federal government scrutiny (see SM), eight companies voluntarily agreed "to work toward eliminating PFOA from emissions and in product content" in the United States by 2015 (*7*). By the time of this agreement between the companies and the U.S. Environmental Protection Agency (EPA), the phase-out of PFOA was already well under way informally (see SM). EPA's PFOA Stewardship Program required the companies to submit annual reports of their progress, although, as a voluntary agreement, it had no enforcement mechanism (*7*). And because the program focused only on reducing and eventually eliminating PFOA emissions and PFOA in product content, it did not in any way address any substitute compounds the companies might develop, use, generate, or release in lieu of PFOA. Toxicity testing and reporting for substitute compounds were simply outside the scope of the PFOA Stewardship Program.

Toxicity testing has revealed reasons for concern about some of these alternatives (*8*, *9*), leading regulatory authorities in at least one U.S. state, New Jersey, to search for replacement as well as legacy PFASs in the environment (*3*, *9*). The report by Washington *et al.*—whose authors are researchers affiliated with EPA and the New Jersey Department of Environmental Protection (DEP)—grew out of that effort. Given the nature of the PFOA Stewardship Program, as well as other features of U.S. chemical regulation that we describe below, it makes sense that the ClPFPECAs the investigators found were previously unknown to them.

Washington *et al.* detected ClPFPECAs in every soil sample they tested from New Jersey, as well as in a stored soil sample taken during earlier research at a location more than 400 km away (*3*). They concluded that their data "strongly suggest atmospheric release" of these compounds from a New Jersey facility of a Solvay S.A. business unit (*3*). They also found these compounds in a previously taken water sample from a river in Italy, which they used to help confirm their identification of the compounds (*3*). The water sample result agreed with prior findings by other researchers who found ClPFPECAs in the same river (*6*). In light of the fairly widespread detection of these compounds in environmental samples, it is reasonable that the researchers suggest that further investigation of these compounds' environmental fate, transport, and degradation is warranted, and that "investigation of whether these ClPFPECAs might be toxic is prudent" (*3*).

PUBLIC TOXICITY INFORMATION

But what can we say right now, based on publicly available information, about "whether these ClPFPECAs might be toxic"? One might think that government regulators could provide some answers for the public. As it turns out, however, trying to trace these compounds through the U.S. and European regulatory systems yields frustratingly unsatisfying answers and reveals a dearth of publicly available research to support such answers as may exist.

In the United States, regulators in California have expressed serious concerns that perfluoroether carboxylic acids—a class that includes the ClPFPECAs (see SM)—"may have similar or higher toxic potency than the longer-chain PFAAs [perfluoralkyl acids] they are replacing" [(*10*), p. 38] and are similarly "recalcitrant to degradation and extremely persistent in the environment" [(*10*), p. 10]. The agency also stated that perfluoropolyethers, in general, may contain as impurities, or upon combustion may release, PFAAs that are persistent, bioaccumulative, and potentially toxic [(*10*), p. 12]. Yet the document expressing these concerns focused primarily on GenX, another chemical in the class, and did not discuss the properties or potential toxicity of ClPFPECAs in particular (*10*). GenX and other PFAS chemicals have also been detected in environmental media at levels that raise regulatory concern (*9*, *11*).

As for Europe, a search by Chemical Abstracts Service (CAS) number 329238-24-6 reveals that the European Chemicals Agency (ECHA) requires classification and labeling of these compounds under the European Classification, Labelling and Packaging (CLP) Regulation. On ECHA's chemical home page, the ClPFPECAs trigger

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five of ECHA's hazard codes: The substance is fatal if swallowed, is fatal in contact with skin (i.e., acutely toxic), causes severe skin burns and eye damage, causes liver damage through prolonged or repeated exposure, and is toxic to aquatic life with long-lasting effects. For 12 other hazard categories, the entries simply read "data lacking." No research to support any of these classifications is cited on or publicly available through the ECHA website.

On the other hand, in 2010 the European Food Safety Authority (EFSA) approved ClPFPECAs for use in the polymerization of anti-stick coatings for repeated-use foodware, subject to restrictions on process quantities and temperatures (*5*). EFSA found the chemical safe for these applications. EFSA concluded that the substance passed a bacterial gene mutation test, an in vitro mammalian cell gene mutation test, and an in vitro mammalian cell chromosome aberration test. The sole source cited was a "dossier" provided by the manufacturer, without any studies that the dossier may have included or cited (*5*). In response to our request for further information under the EU's regulation concerning public access to documents, EFSA provided titles and dates for the three unpublished studies listed in the dossier, but the names and affiliations of the authors were withheld as personal data. As we went to press on 29 May, we were still awaiting a response from EFSA to our further request for access to the full dossier, because the studies cannot be found in the public domain (see SM).

Thus, in our search for toxicity information, we found more questions than answers. There are dire but generalized concerns of the state of California; five hazard classifications listed by ECHA, with "data lacking" for 12 others; and a benign assessment by EFSA, based on limited and unpublished data, with respect to polymerization of foodware coatings. We also checked an enormous chemical-toxicological database maintained by EPA (Comptox), which includes information on some 875,000 chemical substances (far more than the universe of regulated substances). We found an entry for the ClPFPECAs that includes an "executive summary" of the available data in 32 categories of information relevant to toxicity or hazard; no data or values are shown for any of the 32 categories (see SM). Looking beyond government agency websites, we also found no toxicological studies of ClPFPECAs in a literature search.

THE REGULATORY STORY

This scientific inconclusiveness leads to the next obvious set of questions: How could ClPFPECAs appear to be so unstudied and unaccounted for? After all, ClPFPECAs share at least some properties with PFASs that are being phased out (*6, 9, 10*). Society would presumably want to know that substitute chemicals like these are not worse than the chemicals they replace. Shifting focus to the regulatory system, however, yields few definitive answers about the oversight of ClPFPECAs, although it does offer several lessons about the design of our regulatory programs more generally.

The first lesson, just touched on above, is that while regulatory attention is focused on eliminating high-profile chemical risks, less effort appears to be dedicated to analyzing the safety of substitute chemicals used to replace them (*12, 13*). A number of scientists have raised general concerns about the need for rigorous comparative assessments of replacement chemicals, particularly within the PFAS family (*12, 13*). This type of comparative analysis seems particularly appropriate in light of the voluntary phase-out of PFOA, all the more so because EPA has identified about 500 PFAS chemicals sold in U.S. commerce, out of a larger, global list of thousands of such compounds (see SM). However, assessments for PFAS chemicals appear to have been conducted—at best—on an ad hoc basis and primarily through negotiated agreements. The resulting, publicly available research on PFAS chemicals is quite limited. The state of New Jersey reports that out of a list of 900 PFAS chemicals, only 200 chemicals have toxicity data available at all, and even that research is incomplete (*9*). EPA has now instituted more uniform comparative assessment procedures for some PFAS chemicals, but these recently revised procedures apply only to new polyfluoroalkyl chemicals or uses produced after 2015 (see SM). It is of course possible that despite the regulatory vacuum, a comparative analysis was nonetheless performed internally by the manufacturer. If that analysis exists, however, it does not appear to be publicly available.

What about oversight of ClPFPECAs under the U.S. Toxic Substances Control Act (TSCA)? TSCA is a regulatory program originally enacted in 1976 to prevent unreasonable risks caused by chemicals. Under TSCA, makers of "new" chemicals (developed after 1976) must submit a premanufacture notification to EPA (*1*). And the ClPFPECAs certainly seem, on their face, to represent a distinctly "new chemical" developed after 1976 (*4*). A search through EPA's TSCA inventory, however, provides more unsolved mysteries: The ClPFPECA family is not listed (by CAS number) in EPA's public inventory of more than 40,000 registered chemicals (see SM).

It is theoretically possible that the manufacturer simply violated EPA's registration requirements under TSCA, but there are several more likely explanations for why the ClPFPECAs are not listed in EPA's inventory. One is that although the law generally requires premanufacture notification of "new" chemicals, there are multiple exemptions from this registration requirement. It is unclear whether the ClPFPECAs satisfied any of these exemptions, which allow manufacturers to avoid submitting a premanufacture notification, for example, on new chemicals that are long-chain polymers or that are only impurities. But we cannot know for sure, because EPA generally does not provide public tracking of the manufacturers' use of these various exemptions (see SM).

Alternatively, it is possible that the ClPFPECAs are in fact tracked under TSCA, but the chemical is not listed in the public database because the chemical structure was classified by the manufacturer as a protected trade secret (called CBI, for "confidential business information") and removed from public view. Currently, more than 140 unidentified PFAS chemicals in U.S. commerce are classified as CBI, according to EPA (see SM). Once information is stamped by a manufacturer as CBI, only cleared government staff can view the files (*14*). Even the generic names of the CBI chemicals are not made public (*14*). Yet a CBI classification seems inapplicable to the ClPFPECAs because its chemical structure has been published (*4*). In practice, though, a CBI claim remains legally in place until either the manufacturer or EPA officially "declassifies" the claim (*14*). Because more than 10,000 chemicals in the TSCA inventory are classified as CBI (*14*), Congress in 2016 required EPA to review and, if warranted, declassify a subset of CBI chemi-

Where are the data?

The EPA Comptox chemical-toxicological database includes an entry for the ClPFPECAs, but indicates that no data or values are available for any of the categories of information. See (*16*).

- Quantitative Risk Assessment Values
- Quantitative Hazard Values
- Cancer Information
- Reproductive Toxicology
- Chronic Toxicology
- Subchronic Toxicology
- Developmental Toxicology
- Acute Toxicology
- Subacute Toxicology
- Neurotoxicology
- Endocrine System
- Absorption, Distribution, Metabolism, and Elimination
- Fate and Transport
- Exposure
- Adverse Outcome Pathway Information
- Water Quality
- Air Quality
- Occupational Exposure

cals. The agency is still working on this assignment, with about 2000 chemicals left to review (see SM). ClPFPECAs may well be in this queue, but confirming whether they are is not easy; it likely requires a formal request under the federal Freedom of Information Act. We can therefore extract a second lesson about the regulatory system: Some chemicals may fall through the cracks in the public tracking system in the United States, not because they are adequately assessed for toxicity but for other reasons.

Yet just because ClPFPECAs may not be in public view does not mean that the chemicals are out of range of U.S. regulators. Under TSCA, it is possible that even if the product is protected as a trade secret, EPA is actively overseeing the ClPFPECAs. Under this "extensive regulation" scenario, EPA could ask for more testing or other negotiated restrictions as a condition to approving ClPFPECAs under TSCA. Or the agency may be satisfied—after conducting its own analysis—that the risks of ClPFPECAs are not unreasonable. EPA might even impose new restrictions on the manufacture of ClPFPECAs over time if it learns of new "adverse effects," which manufacturers are required by law to report.

Conversely, even if ClPFPECAs were subject to premanufacture regulatory review, it is also possible that EPA decided to pass ClPFPECAs into commerce without much, or any, testing or analysis. Only about 15% of premanufacture notifications for new chemicals submitted to EPA include any health or safety test data at all [(*15*), p. 11], and EPA's own statistics show that only 10% of the new chemicals entering commerce between 1979 and 2016 involved restrictions or testing orders (see SM). In the case of the ClPFPECAs, then, EPA may have been concerned that there was insufficient scientific evidence available at the time to support an order demanding more testing. Under the pre-2016 law, EPA was required, within a brief 90-day period, to produce some evidence of potential risk as a predicate to ordering additional toxicity tests from the manufacturers. This catch-22 resulted in a paucity of testing orders (*1*, *2*). [Congress removed this legal impediment in the 2016 TSCA amendments, but that came too late for the ClPFPECAs (*2*).]

We thus don't know much, if anything, about the regulatory oversight of ClPFPECAs in the United States. This mystery provides yet a third lesson about chemical regulation: For the 40,000-plus chemicals in commerce, the burden of chemical assessment rests almost entirely on a small group of EPA regulators (*1*). As a result, some, perhaps many, chemicals likely fall through the cracks. Indeed, despite the amendments to TSCA in 2016, chemical manufacturers are still not required to anticipatorily test or assess their chemicals as a condition to marketing in the United States (*1*, *2*). Instead, it is the regulators who bear responsibility for identifying the most hazardous chemicals, identifying the relevant scientific literature bearing on toxicity, ordering new tests, and synthesizing and analyzing the available information bearing on the safety of individual chemicals (not to mention determining proper policy responses) (*1*, *2*). Manufacturers' primary role is to serve as respondents. In this role, they not only provide the information that EPA requests, but also have the right to lodge extensive and critical comments on the agency's work. Manufacturers can also sue the agency in court, arguing that some aspect of the agency's analysis might be arbitrary (see SM). And the new powers EPA gained from the 2016 amendments—such as the ability to require additional testing and prioritize chemicals of concern—came with substantial procedural impediments (*2*).

What about Europe? ClPFPECAs are officially registered in two EU regulatory programs. As mentioned above, EFSA approved ClPFPECAs in the manufacture of nonstick coating products (*5*). And ClPFPECAs are listed—along with five hazard classifications—in the EU's notification (CLP) database (see SM). In neither case, however, is the supporting research behind these regulatory findings readily available to the public.

Additionally, in 2005, the European Union implemented REACH, a more aggressive chemical regulatory program than the U.S. TSCA program. Unlike TSCA, REACH requires manufacturers to conduct a comprehensive literature search on the toxicity of each of their chemicals sold above threshold quantities in the European Union. If the existing scientific information proves incomplete under REACH standards, manufacturers are also required to conduct additional toxicity testing (*1*). Yet a search by CAS number returns no results for ClPFPECAs on the European Chemical Agency's website that lists registered REACH chemicals. Perhaps ClPFPECAs are produced in low enough quantities (less than 1 tonne/year) to be exempted from REACH, or perhaps ClPFPECAs satisfy other REACH exemptions, such as those governing impurities or polymers as defined under REACH. Publicly available information again does not resolve this question (see SM).

A LONG WAY TO GO

Public health and environmental concerns led to the phase-out of PFOA and its closest chemical relatives. It seems obvious that in such a scenario, society should want to be reasonably certain that the replacement chemical "cure" is not worse than the phased-out chemical "disease." Yet the researchers from EPA and New Jersey DEP found substitute polyfluorinated compounds, ClPFPECAs, in their environmental samples (*3*). At present, there is little in the public scientific record to indicate whether the environmental dissemination of these substitute PFASs is benign or harmful, and if harmful, how harmful. Our examination of the U.S. and European regulatory programs raises more questions than answers about the extent to which ClPFPECAs are being tracked, studied, and regulated. Certainly the European Union has made more progress than has the United States in this regard (*5*). Still, the toxicological mysteries of ClPFPECAs—and thousands of other potentially toxic chemicals that are regulated (or perhaps not regulated) in ways that remain effectively inscrutable—suggest that we have a long way to go in designing effective and accountable chemical regulation, particularly in the United States. ▩

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SUPPLEMENTARY MATERIALS

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